II. REMARKS

Formal Matters

Claims 7-28 and 30-43 are pending after entry of the amendments set forth herein.

Claims 7-18 and 29-41 were examined and were rejected. Claims 19-28 were withdrawn from consideration.

Claim 29 is canceled without prejudice to renewal.

Claims 42 and 43 are added. Support for new claims 42 and 43 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: paragraph 0036 and SEQ ID NOs:1-23 (paragraphs 0042-0065). Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Jeffrey Parkin for the courtesy of a telephonic interview which took place on March 18, 2008, and which was attended by Examiner Parkin, inventors Melanie Ott and Eric Verdin, and Applicants' representative Paula A. Borden.

During the interview, the rejection under 35 U.S.C.§ 103(a) was discussed. Applicants thank Examiner Parkin for the helpful discussion.

Rejections under 35 U.S.C. § 103(a)

Claims 7-10, 17, 18, 29, and 38 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Deng ((2000) *Virology* 277:278-295; "Deng") in view of Vitellio et al. (U.S. Patent No. 6,419,931; "Vitellio") and Yasuhiko et al. ((2003) *J. Immunol. Methods* 272:161; "Yasuhiko"). Claim 11 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Deng in view of Vitellio and Yasuhiko in view of Kuiken et al. ((2001) HIV Sequence Compendium, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory; "Kuiken"). Claims 12-16 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Deng in view of Vitellio and Yasuhiko and further in view of Rubinstein et al. (U.S. Patent no. 6,447,778; "Rubinstein"). Claims 39-41 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Deng in view of Vitellio and Yasuhiko, and further in view of Frankel et al. ((1988) *Science* 240:4848; "Frankel"). Claims 30-37 were rejected under 35 U.S.C.

§103(a) as allegedly unpatentable over Deng in view of Vitellio, Yasuhiko, and Kuiken. Applicants respectfully traverse the rejections.

Claims 7-10, 17, 18, 29, and 30 over Deng in view of Vitellio and Yasuhiko

The Office Action stated:

1) Deng discloses the presence of acetylated Tat, demonstrates its importance in the viral life cycle, and demonstrates that Tat acetylation at K50 alters the phenotypic properties of the protein;

2) Vitellio provides immunogenic compositions comprising an adjuvant and pharmaceutically acceptable excipients; and

3) Yasuhiko describes preparations of anti-N-epsilon-acetyllysine antibodies and their usefulness in numerous assay formats to detect acetylated proteins.

The Office Action stated that it would have been obvious to prepare immunological reagents, as described by Vitellio, employing the Tat polypeptides of Deng.

Deng discusses acetylation of Tat, and states that acetylation of Tat increases transcription of integrated HIV-1 genome and enhances binding to core histones. There is no teaching or suggestion in Deng that an Ac-Tat polypeptide is immunogenic. There is no teaching or suggestion in Deng of any immunogenic composition comprising an Ac-Tat polypeptide.

None of the secondary references cures the deficiency of Deng. Vitellio discusses immunogenic compositions, but does not disclose or suggest an immunogenic composition comprising an acetylated Tat polypeptide. Yasuhiko discusses antibodies against N-epsilon-acetyllysine. Yasuhiko does not disclose or suggest an immunogenic composition comprising an acetylated Tat polypeptide. As such, Deng, alone or in combination with Vitellio and/or Yasuhiko, cannot render any of claims 7-10, 17, 18, 29, and 30 obvious.

As discussed during the telephone interview, and as elaborated upon below, the literature in the field as of the March 19, 2003 priority date indicated that: 1) Tat is a poor immunogen; and 2) Tat is immunosuppressive. Furthermore, as discussed during the telephone interview, and as elaborated upon below, the observation that acetylated Tat is a good immunogen was unexpected.

The art as of March 19, 2003 teaches away from an immunogenic composition comprising a Tat polypeptide.

As discussed during the telephone interview, the overall view in the literature as of the March 19, 2003 priority date of the instant application was that Tat polypeptides are poorly immunogenic and that Tat polypeptides are immunosuppressive. References that teach that Tat polypeptides are poorly immunogenic or that Tat polypeptides are immunosuppressive teach away from the use of Tat polypeptides in an immunogenic composition. Thus, as March 19, 2003, it would not have been obvious to prepare an immunogenic composition comprising an acetylated Tat polypeptide. The following references are illustrative of the view in the art. Copies of the references discussed below are provided in an Information Disclosure Statement.

Tat was reported to be a poor immunogen.

1) Tähtinen et al. (2001) *Vaccine* 19:2039; "Tähtinen"

Tähtinen is entitled "DNA vaccination in mice using HIV-1 nef, rev and tat genes in self-replicating pBN-vector." Tähtinen describes gene immunization to assess the immunogenicity of HIV-1 Rev and Tat in mice. Tähtinen states that, while Rev elicited proliferative as well as cytotoxic T lymphocyte (CTL) responses, Tat was "a poor immunogen in all respects." Tähtinen, Abstract. Tähtinen states that Tat could not raise a humoral response, and was also poor in raising cell-mediated responses.

2) Lamhamedi-Cherradi et al. (1992) *AIDS* 6:1249; "Lamhamedi-Cherradi"

Lamhamedi-Cherradi is entitled "Qualitative and quantitative analysis of human cytotoxic T-lymphocyte responses to HIV-1 proteins." Lamhamedi-Cherradi describes generating anti-HIV CTL by *in vitro* stimulating of peripheral blood mononuclear cells (PBMC) from seropositive donors, and testing the CLT against HIV proteins, including Tat. Lamhamedi-Cherradi report that Tat was "seldom recognized by CTL." Lamhamedi-Cherradi, Abstract. Figure 1 and Table 1 of Lamhamedi-Cherradi illustrate this point.

Tat was reported to have immunosuppressive activities.

1) Chirmule et al. (1995) *J. Virol.* 69:492; "Chirmule"

Chirmule is entitled "Human Immunodeficiency Virus Tat induces functional unresponsiveness in T cells." Chirmule describes the effect of various HIV polypeptides, including Tat polypeptides, on

proliferative responses of $CD4^+$ T cells. Chirmule reports that synthetic Tat peptides (amino acids 1-86) inhibited proliferative responses of $CD4^+$ T cells in a dose-dependent manner. Chirmule also reports that the synthetic Tat peptides inhibited the anti-CD3-induced proliferative responses of both $CD4^+$ and $CD8^+$ T cells. Chirmule states that, unlike gp120, Tat affects the functional responses of both $CD4^+$ and $CD8^+$ T cells, a phenomenon observed *in vivo* in HIV-infected individuals. Chirmule, page 497, column 2, first incomplete paragraph. Chirmule suggests use of Tat antagonists for the control of HIV infection. Chirmule, page 497, column 2, first incomplete paragraph.

2) Cohen et al. (1999) *Proc. Natl. Acad. Sci. USA* 96:10842; "Cohen"

Cohen is entitled "Pronounced acute immunosuppression *in vivo* mediated by HIV Tat challenge." Cohen reports that the HIV Tat protein is strongly immunosuppressive, both immediately after immunization of mice with soluble Tat protein, and in seroconverting humans. Cohen suggests the use of inactivated, oxidized Tat as a possible vaccine. Cohen, page 10846, column 2, fourth paragraph.

3) Gutheil et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:6594; "Gutheil"

Gutheil is entitled "Human immunodeficiency virus 1 Tat binds to dipeptidyl aminopeptidase IV (CD26): A possible mechanism for Tat's immunosuppressive activity." Gutheil states that it was previously shown that HIV Tat suppresses antigen-induced activation of human T cells (citing Viscidi et al. (1989) *Science* 246:1606). Gutheil reports that Tat binds dipeptidyl aminopeptidase IV (CD26), and suggests that inhibition of CD26 by Tat may be the mechanism underlying the observed immunosuppressive activity of Tat.

4) Agwale et al. (2002) *Proc. Natl. Acad. Sci. USA* 99:10037; "Agwale"

Agwale is entitled "A Tat subunit vaccine confers protective immunity against the immune-modulating activity of the human immunodeficiency virus type-1 Tat protein in mice." Agwale reports that $CD8^+$ T cell responses to gp120 were greatly diminished in mice vaccinated with a bicistronic gp120-Tat DNA vaccine, compared with those induced by a DNA vaccine encoding gp120 alone. Agwale reports that a construct encoding gp120 and a truncated Tat lacking amino acids 30-51 elicited strong $CD8^+$ T cell responses to gp120. Agwale, Abstract, and page 10037, column 2, first paragraph under "Materials and Methods." Thus, if anything, Agwale would argue against use of a Tat polypeptide in an immunogenic composition.

5) Zocchi et al. (1998) *J. Immunol.* 161:2938; "Zocchi"

Zocchi is entitled "HIV-1 Tat inhibits human natural killer cell function by blocking L-type calcium channels." Zocchi reports that treatment of natural killer (NK) cells *in vitro* impairs their cytotoxic activity. Zocchi suggests that exogenous Tat is involved in the impairment of NK cell function during HIV-1 infection.

6) Bennasser and Bahraoui (2002) *FASEB J.* 16:546; "Bennasser"

Bennasser is entitled "HIV-1 Tat protein induces interleukin-10 in human peripheral blood monocytes: involvement of protein kinase C-β11 and –δ." Bennasser states that in HIV-infected patients, production of interleukin-10 (IL-10), a highly immunosuppressive cytokine, is associated with disease progression toward AIDS. Bennasser reports that HIV-1 Tat induces IL-10 production by human monocytes.

7) Gallo (1999) *Proc. Natl. Acad. Sci. USA* 96:8324; "Gallo"

Gallo is entitled "Tat as one key to HIV-induced immune pathogenesis and Pat toxoid as an important component of a vaccine." Gallo discusses the toxicity of HIV Tat, stating that Tat may be an extracellular toxin. Gallo, page 8324, column 1, end of first paragraph; and page 8324, column 2, end of first full paragraph. Gallo discusses the immunosuppressive effects of Tat. Gallo, page 8324, bridging paragraph, columns 1 and 2. Gallo suggests use of an inactivated "Tat toxoid." Gallo, page 8325, column 1, first full paragraph. Gallo further suggests that use of "native Tat" might be hazardous. Gallo, page 8326, column 1, first incomplete paragraph.

The observation that acetylated Tat is a good immunogen was surprising and unexpected.

As discussed during the telephone interview, the observation that acetylation transforms Tat from a poor immunogen to a good immunogen was unexpected. It had previously been shown that Tat is acetylated, and that the acetylation of Tat is involved in Tat function. However, it was not known that acetylation of Tat would transform Tat from a poor immunogen into a good immunogen.

As discussed above and during the telephone interview, it had been amply documented and reported that Tat is poorly immunogenic, and that Tat is immunosuppressive. Those reports would not suggest use of Tat as an immunogen; indeed, those reports indicate quite the opposite.

Claim 11 over Deng in view of Vitellio and Yasuhiko in view of Kuiken

The Office Action stated that Deng, Vitellio, and Yasuhiko do not disclose various HIV-1 isolated encompassed by the sequences set forth in SEQ ID NO:4; and stated that Kuiken provide the complete nucleotide sequences of numerous HIV-1 isolates, including that encompassed by SEQ ID NO:4.

However, as noted above, there is no teaching or suggestion in Deng of any immunogenic composition comprising an Ac-Tat polypeptide. As noted above, neither Yasuhiko nor Vitellio cures the deficiency of Deng. Kuiken merely provides sequences of HIV-1 isolates, and does not disclose or suggest any immunogenic composition comprising an acetylated Tat polypeptide. As such, none of Deng, Vitellio, or Yasuhiko, alone or in combination with Kuiken, renders claim 11 obvious.

Furthermore, as noted above, the art as of the March 19, 2003 priority date teaches away from use of a Tat polypeptide as an immunogenic. As such, the art teaches away from an immunogenic composition comprising an acetylated Tat polypeptide.

Claims 12-16 over Deng in view of Vitellio and Yasuhiko and further in view of Rubinstein

The Office Action stated that Rubinstein provides immunogenic compositions comprising polypeptides linked to a carrier; and states that it would have been obvious to conjugate or link Tat to a carrier as described by Rubinstein.

However, as noted above, there is no teaching or suggestion in Deng of any immunogenic composition comprising an Ac-Tat polypeptide. As noted above, neither Yasuhiko nor Vitellio cures the deficiency of Deng. Rubinstein merely discusses linking a polypeptide to a carrier, and does not disclose or suggest any immunogenic composition comprising an acetylated Tat polypeptide. As such, none of Deng, Vitellio, or Yasuhiko, alone or in combination with Rubinstein, renders any of claims 12-16 obvious.

Furthermore, as noted above, the art as of the March 19, 2003 priority date teaches away from use of a Tat polypeptide as an immunogenic. As such, the art teaches away from an immunogenic composition comprising an acetylated Tat polypeptide.

Claims 39-41 over Deng in view of Vitellio and Yasuhiko in view of Frankel

The Office Action stated that Frankel demonstrates that wildtype Tat exists in a multimeric configuration; and stated that it would have been obvious to prepare immunological reagents comprising multimeric forms of Tat.

However, as noted above, there is no teaching or suggestion in Deng of any immunogenic composition comprising an Ac-Tat polypeptide. As noted above, neither Yasuhiko nor Vitellio cures the deficiency of Deng. Frankel merely discusses the observation of metal-linked dimeric Tat, and does not disclose or suggest any immunogenic composition comprising an acetylated Tat polypeptide. As such, none of Deng, Vitellio, or Yasuhiko, alone or in combination with Frankel, renders any of claims 39-41 obvious.

Furthermore, as noted above, the art as of the March 19, 2003 priority date teaches away from use of a Tat polypeptide as an immunogenic. As such, the art teaches away from an immunogenic composition comprising an acetylated Tat polypeptide.

Claims 30-37 over Deng in view of Vitellio, Yasuhiko, and Kuiken

The Office Action stated that it would have been obvious to prepare immunological reagents comprising multiple copies of Tat, particularly from different clades.

However, as noted above, there is no teaching or suggestion in Deng of any immunogenic composition comprising an Ac-Tat polypeptide. As noted above, none of Yasuhiko, Vitellio, and Kuiken cures the deficiency of Deng. As such, none of Deng, Vitellio, or Yasuhiko, alone or in combination with Kuiken, renders any of claims 30-37 obvious.

Furthermore, as noted above, the art as of the March 19, 2003 priority date teaches away from use of a Tat polypeptide as an immunogenic. As such, the art teaches away from an immunogenic composition comprising an acetylated Tat polypeptide.

Conclusion as to the rejections under 35 U.S.C. §103(a)

Applicants submit that the rejections of the claims discussed above under 35 U.S.C. § 103(a) have been adequately addressed in view of the remarks set forth above. The Examiner is thus

respectfully requested to withdraw the rejections.

Rejection under 35 U.S.C. §112, first paragraph

Claims 34-36 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action stated that claims 34-36 reference Tat polypeptides comprising amino acids 1-45, 55-72, or both 1-45 and 55-72; and stated that the disclosure fails to provide support for the claimed limitations. Applicants respectfully traverse the rejection.

Support for claims 34-36 is found in the specification at, e.g., paragraph 0095, which states:

> In other embodiments, a subject composition comprises one or more acetylated Tat polypeptides and in addition, comprises a Tat polypeptide that is non-acetylated. A subject acetylated Tat polypeptide can be formulated together with one or more polypeptides comprising an amino acid sequence from about **amino acid 1 to about amino acid 45**, from about amino acid 5 to about amino acid 40, from about amino acid 10 to amino acid 35, from about amino acid 15 to about amino acid 30, from about amino acid 20 to about amino acid 25, from about amino acid 1 to about amino acid 10, from about amino acid 10 to about amino acid 20, from about amino acid 20 to about amino acid 30, or from about amino acid 30 to about amino acid 40, or a fragment of any size from about amino acid 1 to about amino acid 45 of an immunodeficiency virus Tat protein. A subject acetylated Tat polypeptide can be formulated together with one or more polypeptides comprising an amino acid sequence **from about amino acid 55 to about amino acid 72**, e.g., from about amino acid 55 to about amino acid 60, from about amino acid 55 to about amino acid 65, or from about amino acid 60 to about amino acid 72 of an immunodeficiency virus Tat protein. Thus, in some embodiments, a subject composition comprises at least a first acetylated Tat polypeptide; and a second polypeptide comprising a sequence of **amino acid 1 to amino acid 45 and/or amino acids 55 to about amino acid 72 of a Tat polypeptide**.
>
> Specification, paragraph 0095, bold added.

As such, the specification provides support for claims 34-36.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 34-36 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-296.

Respectfully submitted,
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Date: March 21, 2008

By: /Paula A. Borden, Reg. # 42,344/
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